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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,939	12/20/2000	Cesare Galli	P66004USO	8697

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EXAMINER	
CROUCH, DEBORAH	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/647,939	GALLI ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 5, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 5, 2007 has been entered. Pending claims are 19-21 and 26-28

The declaration by Cesare Galli, filed June 5, 2007, has been considered but is not persuasive for reasons set forth below.

The rejections made under 35 U.S.C. § 112, second paragraph made in the office action mailed December 6, 2006 are withdrawn in view of applicant's amendments to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-21 and 26-28 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons set forth in the office action mailed June 12, 2006 and December 6, 2006. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is repeated below.

Claims 19-21 and 26-28 are to a method of reconstructing a mammalian embryo comprising reconstructing a first generation embryo comprising transferring a mononuclear cell isolated from the blood or natural secretion of a mammal, or an isolated nucleus of said mononuclear cell, into the cytoplasm of an enucleated oocyte, activating the oocyte,

developing the embryo to a stage where it can transferred to a uterus, and transferring a cell isolated from the first generation embryo, or an isolated nucleus of said cell into the cytoplasm of an enucleated oocyte to form a second generation embryo, a method of reconstructing a mammalian embryo comprising reconstructing a first generation embryo comprising transferring a mononuclear cell from the blood or natural secretion of a mammal or a nucleus isolated from a mononuclear cells to an enucleated oocyte, preparing fetal fibroblast cultures from the first generation embryo and transferring cells from said fetal fibroblast cultures to an enucleated oocyte suitable recipient to form a second generation embryo, where the fetal fibroblasts are genetically modified, and permitted the development of the embryo to term, and methods of producing a mammal comprising developing to term the second generation embryo..

Claims 19-21 are not enabled because at the time of filing, the art regarded nuclear transfer, using a lymphocyte or leukocyte to be unpredictable. Galli teaches the production of one calf by repeat nuclear transfer, where the original nucleus was isolated from peripheral blood leukocytes (page 166, col. 1, lines 10-14). Repeat nuclear transfer, as disclosed in Galli, is the formation of an initial reconstructed embryo, isolating a blastomere from the resulting morulae, and transferring the blastomere into an enucleated MII oocyte (page 163, col. 1, parag. 3, to col. 2, lines 16). Galli states for successful nuclear transfer 2 steps in their protocol are essential: precise optimization of the size of the pipette and use of a piezostepper to rupture the oocyte membrane prior to nuclear injection (page 168, col. 1, parag. 1, lines 11-17). With mice, at the time of filing, nuclear transfer using nuclei from leukocytes and lymphocytes failed to produce mice (page 382, col. 2, parag. 1, lines 1-3 and 5-8; and page 380, Table 3). Wakayama states this result maybe due to gene rearrangement in lymphocytes, where some genes are poorly or not expressed because of the rearranged genome (page 382, col. 2, parag. 1, lines 13-17). Hochedlinger teaches the

production of mice by nuclear transfer using B- and T-cell nuclei as nuclear donor by a two-step procedure where ES cells were derived from cloned blastocyst and injection of the ES cell into a tetraploid host blastocyst (page 1035, col. 1, parag. 2, lines 3-8). Hochedlinger supports statements made by Wakayama in stating reprogramming B- and T-cell nuclei are less efficient (page 1037, col. 2, parag. 2, lines 11-14). Claims 19-21 lack enablement because lymphocyte nuclei were regarded by the art as not contributing to the development of an animal by nuclear transfer without particular methodologies not disclosed in the specification. Thus, to make the claimed invention, the skilled artisan would have needed additional method steps not disclosed, and thus would have been required to make essential steps before achieving animal production from lymphocyte nuclear donors. Therefore, it would have been regarded as unpredictable to produce a human or nonhuman animal using B- or T-cell as nuclear donors at the time of filing.

In addition, claims 19-21 are not enabled because at the time of filing, the art regarded the production of nonprimate mammals by nuclear transfer as not enabled. The cloning of monkeys by nuclear transfer had been successful when embryonic cells were the nuclear donors, not when somatic cells were used as nuclear donor (Mitalipov, abstract). Mitalipov further states, clearly, that somatic cell cloning, as is part of the present methods, has not been accomplished in primates (Mitalipov, page 1367, col. 2, parag, 3, lines 1-3). Simerly, states that in rhesus monkey NT units, DNA and microtubule imaging showed disarrayed mitotic spindles with misaligned chromosomes, which resulted in unequal chromosome segregation and aneuploid embryos (page 297, col. 2, parag. 1, lines 5-11). The art, therefore, at the time of filing clearly disclosed the unpredictable nature of nuclear transfer using a primate somatic cell as nuclear donor.

Therefore, at the time of filing, the skilled artisan would have needed to conduct an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

Declarant Galli states there is no requirement to use a piezostepper or to optimize the pipette size for nuclear transfer. Declarant states all that is necessary is that the donor cell or nucleus is introduced into the oocyte cytoplasm. Declarant also states Galileo was produced by the direct injection method. Declarant relates the piezostepper may improve the method of microinjection, but "you can still succeed, as we did, without them." Declarant's statements are not persuasive.

The paper, Galli et al, Cloning, 1999, Vol. 1, No. 3, pp. 161-170, clear states the birth of Galileo was due to the use of a piezostepper. To quote "precise optimization of the size of the pipette (to disrupt the leukocyte membrane without damaging the nucleus) and the use of a piezostepper to facilitate cytoplast membrane disruption before nuclear injection are essential for the successful reconstruction of embryos" (page 168, col. 1, parag. 1, lines 11-17). Further, Galli describes both pipette size optimization and the piezostepper as the microinjection device in the method that lead to the birth of Galileo (Galli, page 163, col. 1, parag. 1, lines 3-7 and lines 11-13; and page 166, col. 1, lines 10-14). The clear teaching from Galli is that the particular steps, pipette size optimization to disrupt cell membranes and microinjection by a peizostepper, are required for nuclear transfer where the donor is a leukocyte or monocyte. Thus the claims, in view of Galli, are not enabled with requirements that the pipette size be optimized for leukocyte membrane rupture and use of a piezostepper. When a leukocyte is the nuclear donor, apparently, particular methodologies are necessary ensure a term birth. This is supported by the failures of both Wakayama et al and Hochedlinger et al, as stated above. Although, neither Wakayama nor Hochedlinger use recloning method of the claims, there is no evidence of

record that recloning without the optimization of the micropipette or the use of a peizostepper would yield a cloned mammal from a leukocyte/mononuclear cell as nuclear donor. With mice, at the time of filing, nuclear transfer using nuclei from leukocytes and lymphocytes failed to produce mice (page 382, col. 2, parag. 1, lines 1-3 and 5-8; and page 380, Table 3). As the present specification so aptly demonstrates, nuclear transfer is highly unpredictable in the best of circumstances. It is not possible to tell without evidence what is necessary for a predictable result and what is not. Optimization of micropipette size and the peizostepper from Galli et al appear to be essential. It is noted the claims state "transferring," and not "microinjection."

Applicant argues neither Wakayama et al or Hochedlinger et al use applicant's method, and thus are not relevant to the enablement of the claims. This argument is not persuasive.

As stated above, Wakayama and Hochedlinger each teach nuclear transfer where the donor cell is a leukocyte yielded no cloned mice, unless, as in the case of Hochedlinger, the extra step of embryo aggregates were used. It not possible to tell what is needed and what is not needed to make the claimed method predictable.

Applicant argues the examiner's argument over primate cloning is irrelevant because insufficient number of oocytes were used. This argument is not persuasive.

Applicant has made an allegation that if more primate oocytes were used, then a cloned primate would be produced. However, applicant has not provided any authority for such a statement. Without supporting evidence, the teachings of Mitalipov et al and Simerly stand. Mitalipov clearly states somatic cell nuclear transfer was unsuccessful in the production of cloned monkeys (Mitalipov, abstract). Mitalipov further states, clearly, that somatic cell cloning, as is part of the present methods, has not been accomplished in primates (Mitalipov, page 1367, col. 2, parag, 3, lines 1-3). Thus, the art supports the lack

of enablement in producing cloned mammals. Simerly offers a reason why primate cloning is unpredictable within the guidance of 35 U.S.C. § 112, first paragraph. The response provided is insufficient to overcome the rejection.

Applicant argues in the declaration by Dr. Galli, it is stated the calf of the specification was made without pipette size optimization or a peizostepper. Applicant argues the embryo that produced Galileo was obtained by direct injection, and there are several approaches to direct injection known in the art. These arguments are not persuasive.

As stated above, there is conflict between the declaration and the publication regarding the production of Galileo. While the declarant says direct injection was used, the publication states the piezostepper and micropipette size optimization were essential. Thus, Galileo's production, according to the above cited publication is due to these essential steps. Steps essential to the enablement of the claimed invention must be included in the claims. Thus. only direct injection by piezostepper using a micropipette optimized to rupture the leukocyte cell membrane is enabled. Thus, the example is the specification is not the method used to produce Galileo. That method is much narrower as evidenced by Galli et al.

The claims are free of the prior art. At the time of filing the prior art did not teach or suggest a method of reconstructing a mammalian embryo comprising reconstructing a first generation embryo comprising transferring a mononuclear cell from the blood or natural secretion of a mammal to a suitable recipient and transferring a cell from the first generation embryo of a suit a suitable recipient to form a second generation embryo, and a method of reconstructing a mammalian embryo comprising reconstructing a first generation embryo comprising transferring a mononuclear cell from the blood or natural secretion of a mammal to a suitable recipient, preparing fetal fibroblast cultures from the first generation

embryo and transferring cells from said fetal fibroblast cultures to a suitable recipient to form a second generation embryo, and where the fetal fibroblasts.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 6:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

July 27, 2007